REMARKS

This amendment is in response to the Office Action, dated August 25, 2005, ("Office Action"). It is respectfully submitted that the application is in condition for allowance. Claims 10, 21 and 29-56 were withdrawn from consideration by virtue of Examiner's restriction requirement and Applicant's election. Claims 1-9, 11-20 and 22-28 were rejected. Claims 1, 12, 23, 26, 29 and 32 have been amended. Claims 10, 21 and 29-34 have been withdrawn, without prejudice, by virtue of the present amendment. Claims 35-56 have been canceled, without prejudice, by virtue of the present amendment. New claims 67-62 have been added. Following entry of the present amendment, amended claims 1-9, 11-20, 22-28 and new claims 57-62 are pending. No new matter has been added. Allowance and reconsideration of the application in view of Applicant's amendment and the ensuing remarks are respectfully requested. Applicant reserves the right to pursue other aspects of the present invention in later filed applications.

Claims 1, 12, 23, 26, 29 and 32 have been amended to more particularly point out that which Applicant regards as his invention. Claims 1, 12, 23, 26, 29 and 32 as suggested by the Examiner, have been amended such that they describe a "method of treating androgen-independent prostate cancer in a mammal in need thereof..." Support for these amendments may be found throughout the specification; for example, on p. 5, lines 16-20 and throughout the Examples. Notwithstanding the amendment to claims 1, 12, 23, 26, 29 and 32 Applicant reserves the right to pursue other aspects of the present invention in later filed applications.

New claims 57-62 have been added. Support for these claims can be found throughout the specification. For example, support for these clams can be found on pages 5-8, 11-12 (examples 1, 2 and 3), and figures 1A and 1B.

Examiner acknowledged, and Applicant affirms, the election, with traverse, of the embodiment of the instant invention including the compound and its prodrug with the

C=O constituent of R_5 for the treatment and prevention of **androgen-independent prostate cancer**, claims 1-9, 11-20, 22-28, 35-43, 45-54 and 56.

Examiner withdrew claims 10, 21, 29-34, 44, and 55 from further consideration as not being drawn to an elected invention. Examiner also withdrew claims 35-56 from further consideration, as being drawn to a nonelected invention.

Examiner objected to claims 1-9, 12-20, 23-25 and 27-28 as containing non-elected subject matter. Applicant respectfully submits that Claims 11, 22, 23-25, and 26-28, as amended are allowable; therefore, generic claims 1-9, 12-20, encompassing additional species are allowable. Applicant is also unclear as to the reason for Examiner to object to claims 23-25 and 27-28 as these claims do not contain nonelected subject matter. Claims 23-25 and 27-28 are directed to treating **androgen-independent** prostate cancer. Although there is no "R_5" identified in Claims 23-25 and 27-38, the analogous position of the subsistent of R_5 is **C=O** in Claims 23-25 and 27-28. Thus, Applicant respectfully requests Examiner to withdraw this objection. As amended, claims 1-9, 12-20, are drawn to elected subject matter. Thus, Applicant respectfully submits that amended claims 1-9, 12-20, 23-25 and 27-28 are allowable, and therefore respectfully requests that Examiner withdraw this objection.

Examiner rejected Claims 1-9, 11-20 and 22-28 under 35 U.S.C. §112, second paragraph, as being indefinite. Examiner stated that "the intent of the method is not clear since the method is to treating a mammal and not to treating androgen-independent prostate cancer." Examiner suggested amending the claims to recite, "A method of treating androgen-independent prostate cancer in a mammal in need thereof..."

Examiner also stated that Applicant specifically defined "androgen-independent" contrary to its ordinary meaning. Examiner cited Diaz *et al.*, and stated, "the term "androgen-independent" in claims 1, 12, 23, and 26 is used by the claim to mean "hormone refractory prostate cancer" ...while the accepted meaning of "androgen-independent prostate cancer (AIPC) implies a potential for patients to respond to a secondary hormonal measure, while the term "hormone-resistant prostate cancer"

(HRPC) includes patients who do not respond to various hormone treatments or who have progressed following these treatments and would not be expected to respond to another. In the Crawford "D" classification, both would be included in the D3 category, with D3S and D3I indicating hormonally sensitive and hormonally resistant cases, respectively." With respect to Claims 1-9, 11-20 and 22-28, these rejections under 35 U.S.C. §112, second paragraph, are respectfully traversed.

First, Applicant has adopted Examiner's suggestion and Claims 1-9, 11-20 and 22-28 have been amended to recite, "A method of treating androgen-independent prostate cancer in a mammal in need thereof..." Applicant therefore respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

Second, Applicant respectfully submits that Applicant did not specifically define "androgen-independent" contrary to its ordinary meaning and the term "androgen-independent" is not indefinite. Applicant's reference to "hormone refractory prostate cancer" on page 2 of the Specification merely acknowledges that androgen-independent prostate cancer may also commonly be referred to as hormone refractory prostate cancer. In fact, page 2 of Applicant's Specification also states that androgen-independent prostate cancer "does not depend on androgens for its growth; as a result, hormone ablative therapy has little effect on it." This definition is consistent with a definition provided by Diaz *et al.* "...androgen-independent phase [is] where the initial androgen deprivation regime no longer controls the tumor." *See* Diaz *et al.* at page 365. Additionally, Applicant further described what is intended by the use of the term "androgen-independent". "...[C]ompounds of Formula I ...may be used to treat androgen-independent prostate cancer; that is, such compounds may be used to treat *cancers that lack androgen receptors or otherwise do not depend on androgens for their growth*." *See* Specification at p. 5 lines 16-20 (emphasis added). Moreover, Applicant respectfully submits that Examiner's reliance of Diaz *et al.* for defining the term "androgen-independent prostate cancer" with reference to the Crawford "D" Classification is misplaced. According to Diaz *et al.* the Crawford "D" Classification is *not widely used.* (*See* Diaz *et al.* "Management of Androgen-Independent Prostate Cancer," *Cancer Control* 11(6):364-373 (2004), hereinafter "Diaz", p. 365; emphasis

added.) Furthermore, Applicant submits that one of skill in the art would have no difficulty discerning the meaning of this term in the context of the claim based on its normal use.

Thus, the term "androgen-independent" is sufficiently clear as to describe the subject matter of the claim with reasonable particularity and distinctness, and is therefore sufficiently definite for purposes of 35 U.S.C. §112, second paragraph. Applicant respectfully requests reconsideration and withdrawal of this rejection.

Examiner rejected claims 1-9, 11-20 and 22-28 under 35 U.S.C. §103(a) as being unpatentable over EP 0 652 004 (hereinafter "the '004 Publication") in view of Diaz *et al.* and Raghow *et al.* ("Toremifene Prevents Prostate Cancer in the Transgenic Adenocarcinoma of Mouse Prostate Model," *Cancer Research* 62:1370-1376 (2002), hereinafter "Raghow"). Examiner found that the '004 Publication disclosed that "the instant compound is useful for treating resistant neoplasms, including prostate cancer" and that Diaz' definition of AIPC "implies a potential for patients to respond to a secondary hormonal measure." The Examiner concluded that "it would be obvious...to use the compound of '004 to yield the instant method, because '004 discloses that the instant compound is useful for treating resistant neoplasms...[including] those for whom a primary measure was no longer effective." Examiner, with reference to the dependent claims, stated that "... it is within the skill of the artisan to determine the optimum dosage and route of administration." Furthermore, Examiner stated that Raghow "discloses that teremifene [sic] is an antiestrogen that is useful in treating prostate cancer [and] [i]n the absence of unexpected results no unobviousness is seen in using two compounds together..." Examiner further noted that Clinical Trials ("Clinical Trials: Phase II Randomized Study of Toremifene Followed by Radical Prostatectomy in Treating Patients with Stage I or II Adenocarcinoma of the Prostate," www.clinicaltrials.gov/clinicaltrials/PCI-00-105, 1-3, (2001), hereinafter "Clinical Trials") disclosed the use of toremifene to treat prostate cancer. With respect to claims 1-9, 11-20 and 22-28, this rejection is respectfully traversed.

Three basic criteria must be met to establish a prima facie case of obviousness: (1) "there must be some suggestion or motivation...to combine reference teachings," (2)

"there must be a reasonable expectation of success," and (3) *the prior art references "must teach or suggest all the claim limitations*." MPEP §2142 (emphasis added). Furthermore, the suggestion or motivation to combine reference teachings must be found in the prior art and cannot be based solely on hindsight. MPEP §2145(X)(A). A reconstruction based on hindsight reasoning may be proper if takes account only knowledge which was within the level of ordinary skill in the art at the time of the claimed invention was made and does not include knowledge gleaned from applicant's disclosure. *See In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). Furthermore, while motivation to combine the references need not be "express," it nonetheless needs to be based on the prior art. *See Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1276 (Fed. Cir. 2004).

I. The References Do Not Teach or Suggest all of the Claim Limitations

The '004 Publication indicates that the compound is to reverse resistance or to inhibit the resistance of resistant neoplasms, that is, "will cause the neoplasm to be more sensitive to the appropriate chemotherapy." (*See* the '004 Publication p. 4, lines 33-35.) Indeed, the '004 Publication specifically contemplates the use of a chemotherapeutic agent in combination with the compound. (*See* the '004 Publication, p. 5, lines 48-52.) In sharp contrast, Claims 1-9, 11-20 and 22-28 of the present application are directed to the use of the inventive compounds to directly treat AIPC -- the compounds need not be used concurrently with chemotherapeutic agents, as described in the '004 Publication. In fact, as opposed to androgen-*dependent* prostate cancer ("ADPC"), androgen-*independent* prostate cancer cannot generally be treated with conventional cancer therapies, such as chemotherapy. Thus, one skilled in the art would readily appreciate that the '004 Publication is directed to forms of cancer, such as ADPC, that are clinically distinct from AIPC. Examiner concedes that the '004 Publication does not recite androgen-*independent* prostate cancer; a conclusion with which Applicant entirely agrees.

Moreover, Diaz merely describes AIPC as implying a potential for patients to respond to a secondary hormonal measure. (*See* Diaz, p. 365.) Diaz also states that "secondary hormone therapies are *palliative* in nature and have *not* been associated

with survival benefits." Furthermore, Diaz's disclosure regarding secondary hormone therapies consists of second-line antiandrogens, adrenal androgen inhibition, and compounds with *estrogenic* properties. (*See* Diaz, p. 366-367, emphasis added.) Therefore, Diaz can only be interpreted to support the proposition that compounds unlike those of the present invention may be used as a secondary measure for the palliative care of AIPC patients.

In marked contrast, Applicant's invention relates to the primary (*i.e.*, rather than "secondary") therapeutic treatment (*i.e.*, not merely palliative care) of AIPC with the inventive compounds. In fact, as detailed in the Specification, Applicant's data shows survival benefits and other beneficial results in AIPC patients based on this treatment regime. By way of example, in Example 1 of the Specification, Applicant's data illustrates that an AIPC patient treated with raloxifene showed improvement in his bone scan, and there was tumor stabilization in the majority of the AIPC patients treated with raloxifene. (*See generally* Specification pp. 11-23, particularly examples 1, 2, and 14.) Moreover, Applicant's inventive compounds are known for their *antiestrogenic* properties, and thus are not within the compounds contemplated by Diaz for secondary hormonal treatment. (*See* Specification p. 5, line 16 to p. 6, line 2.)

Raghow and Clinical Trials describe the use of antiestrogen to treat prostate cancer. However, neither Raghow nor Clinical Trials disclose the use of toremifene to treat androgen-*independent* prostate cancer, which, as noted above, is clinically distinct from ADPC. Thus, based on the aforementioned combination of references, Applicant respectfully submits that the claimed invention is not rendered obvious, because, at a minimum, the references do not teach or suggest all the claim limitations; specifically, the use of the claimed compound for treating AIPC.

II. There is No Reasonable Expectation of Success in Combining the Prior Art References

Applicant respectfully submits that the prior art does not provide a reasonable expectation of success for the use of the instant compounds to treat AIPC. The treatment regimes in the prior art relate to a different form of cancer – androgen-dependent prostate cancer. Examiner concedes that the '004 reference does not relate

to androgen-independent prostate cancer. Raghow and Clinical Trials also only relate to ADPC.

Diaz discusses management options for AIPC, however, the management options are for palliative care and are not actually treating AIPC, that is, the management options do not slow down and/or lessen the disease. Diaz recognized that secondary hormonal measures are palliative in nature. (*See* Diaz, page 366.)

Furthermore, tamoxifen, an antiestrogen similar to raloxifene, had exhibited no effect on AIPC in previous clinical studies. (*See* Specification, page 5, line 20 to page 6, line 1.) Based on these clinical studies, one skilled in the art would not have reasonably expected the instant compounds to be successful in treating AIPC. In fact, one skilled in the art would find it surprising that the instant compounds would be able to treat AIPC.

Therefore, there would be no reason to believe that the combination of the cited references would provide a successful treatment for AIPC with the claimed compounds.

III. There is No Suggestion or Motivation to Combine the References

Applicant respectfully submits that the combination of the aforementioned references is improper because there is no suggestion or motivation for the skilled practitioner to combine the references' teachings. The '004 Publication merely describes the use of the inventive compounds to reverse the resistance of certain resistant neoplasms -- as noted by Examiner, it does not mention AIPC. Diaz discloses that *secondary* hormone therapies are *palliative* in nature with respect to AIPC. Finally, Raghow and Clinical Trials merely describe the use of toremifene to treat ADPC in mice and humans, respectively.

Applicant respectfully submits that Examiner's conclusion that there is a suggestion or motivation to combine the references is based on improper hindsight reasoning. The aforementioned references do not expressly suggest or provide a motivation to combine the references. AIPC and ADPC are clinically distinct types of prostate cancer. One skilled in the art would appreciate that treatment options for ADPC cannot be effectively used to treat AIPC. The suggestion or motivation to

combine the aforementioned references must be derived from the prior art and not based on applicant's disclosure.

The '004 Publication discloses raloxifene as a compound to reverse the resistance of certain resistant neoplasms, thereby making them more susceptible to chemotherapy. Moreover, as recognized by Examiner, the '004 Publication does not disclose that raloxifene is effective in making AIPC more susceptible to chemotherapy and it does not disclose that raloxifene is effective in treating AIPC. As such, one of skill in the art would neither look to the '004 Publication for a method to treat AIPC, nor combine the '004 Publication with a reference that discusses ADPC to devise a method to treat AIPC.

Diaz discloses management options for AIPC and implies that patients with AIPC have potential to respond to secondary hormonal measures. Diaz discloses that *secondary* hormone therapies are *palliative* in nature with respect to AIPC. Diaz's disclosure regarding secondary hormone therapies consists of second-line antiandrogens, adrenal androgen inhibition, and compounds with *estrogenic* properties. (*See* Diaz, p. 366-367, emphasis added.) Diaz does not disclose that an antiestrogen, such as one of the claimed compounds, may be used for palliative measures. Moreover, the prior art has shown that antiestrogens similar to the instant compounds are not effective for treating AIPC. (*See* Specification, page 5, line 20 to page 6, line 1.) Thus, one skilled in the art would not look to using secondary hormone therapies (known for their palliative effects) to treat AIPC for curative or life prolonging purposes. Furthermore, one skilled in the art would not combine Diaz with a reference that discusses ADPC, for example the'004 Publication, Raghow and Clinical Trials, to create a treatment for AIPC.

Raghow and Clinical Trials disclose the use of toremifene to treat ADPC, not AIPC. Again, one skilled in the art would not combine Raghow or Clinical Trials with Diaz since ADPC and AIPC are clinically distinct types of prostate cancer.

Accordingly, one skilled in the art would not have been motivated to combine the '004 Publication, Diaz, Raghow and Clinical Trials.

In sum, the cited references do not teach each element of Applicant's claims, as amended; the references do not provide any reasonable expectation that the use of the inventive compounds would be successful in treating AIPC; and Examiner has not shown any motivation in the prior art to combine the references. Furthermore, because Applicant's claimed methods are patentable, the dependent claims are similarly patentable.

In light of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

Examiner rejected claims 1-9, 11-20 and 22-28 under 35 U.S.C. §103(a) as being unpatentable over Neubauer *et al.* ("Raloxifene (LY156758) Produces Antimetastatic Responses and Extends Survival in the PAIII Rat Prostatic Adenocarcinoma Model," *The Prostate* 27:220-229 (1995), hereinafter "Neubauer") in view of Raghow *et al.* Examiner found that Neubauer disclosed that "the instant compound is a physiological antagonist of androgen and is used to treat prostate cancer." Examiner stated that Neubauer disclosed that "the instant compound is also effective in the treatment of hormone-insensitive human prostate cancer [and] [i]t would be obvious to use the compound of Neubauer to yield the instant method." Once more, Examiner, with reference to the dependent claims, stated that "... it is within the skill of the artisan to determine the optimum dosage and route of administration." Furthermore, Examiner again cited Raghow and Clinical Trials as teaching the use of an estrogen lowering drug to treat prostate cancer. With respect to claims 1-9, 11-20 and 22-28, this rejection is respectfully traversed.

Again, three basic criteria must be met to establish a prima facie case of obviousness: (1) "*there must be some suggestion or motivation...to modify the reference or to combine reference teachings*," (emphasis added) (2) "there must be a reasonable expectation of success," and (3) *the prior art references "must teach or suggest all the claim limitations*." MPEP §2142 (emphasis added). Furthermore, the suggestion or motivation to combine reference teachings must be found in the prior art and cannot be based solely on hindsight. MPEP §2145(X)(A). A reconstruction based on hindsight reasoning may be proper if takes account only knowledge which was within

the level of ordinary skill in the art at the time of the claimed invention was made and does not include knowledge gleaned from applicant's disclosure. *See In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). Furthermore, while motivation to combine the references need not be "express," it nonetheless needs to be based on the prior art. *See Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1276 (Fed. Cir. 2004).

I. There is No Suggestion or Motivation to Modify the References

Applicant respectfully submits that the modification of Neubauer is improper because there is no suggestion or motivation for the skilled practitioner to modify the reference's teachings. In fact, Neubauer provides evidence of nonobviousness of the present inventive methods.

Neubauer discloses raloxifene's effectiveness on reducing metastasis in rat prostatic adenocarcinoma. However, Neubauer states that raloxifene did not inhibit tumor growth. (*See* Neubauer, pp. 225 and 227.) In contrast, Applicant's data shows a reduction in tumor size in mice treated with raloxifene. (See Specification pp 11-12, Example 1, 2 & 3, Figure 1.) The present inventive methods may be used as primary treatment methods for AIPC, for example, to stabilize or reduce the tumor size. This is shown, for the first time, in the present invention. Indeed, Neubauer's disclosure that raloxifene has no effect on tumor growth provides evidence of nonobviousness of the present inventive methods. Consequently, Neubauer does not render the instant methods obvious.

Moreover, Neubauer also asserts that the antimetastatic effects were not mediated by estrogen receptors. (*See* Neubauer, p. 228.) Applicant's data demonstrates that prostate cancer cells express the beta isoform of estrogen receptors, and Applicant believes that the mechanism of action of the compound is signaling through the beta isoform of the estrogen receptor. (See Specification, p 6, lines 3-7, and Figure 2.) Consequently, rather than making the present invention obvious, Neubauer has mischaracterized and therefore misunderstood the pathophysiology of the disease and the effect of this drug.

II. There is No suggestion or Motivation to Combine the References

Applicant submits that the combination of the aforementioned references is not proper because there is no suggestion or motivation for the skilled practitioner to combine the refernces' teachings. Once more, Raghow and Clinical Trials disclose the use of an antiestrogen to treat prostate cancer. However, neither Raghow nor Clinical Trials disclose the use of toremifene to treat androgen-independent prostate cancer, which is clinically distinct from prostate cancer that is dependent on androgens. As such, one skilled in the art would not look to combining Raghow and/or Clinical Trials with Neubauer to provide the present inventive methods to treat androgen-independent prostate cancer.

III. There is No Reasonable Expectation of Success

Applicant respectfully submits that the prior art does not provide a reasonable expectation of success for the use of the instant compounds to treat, (*e.g.*, stabilize or reduce tumor growth) AIPC.

Neubauer states that raloxifene did not inhibit tumor growth. (*See* Neubauer, pp. 225 and 227.) In contrast, Applicant's data shows a reduction in tumor size in mice treated with raloxifene. (*See* Specification pp 11-12, Example 1, 2 & 3, Figure 1.) The present inventive methods may be used as primary treatment methods for AIPC; for example, to stabilize or reduce the tumor size. This is shown, for the first time, in the present invention. Indeed, Neubauer's disclosure that raloxifene has no effect on tumor growth dispels any reasonable expectation of success in using the instant compounds to treat (*e.g.*, stabilize or reduce) AIPC tumors. Consequently, this provides further evidence of nonobviousness of the present inventive methods.

IV. The References Do Not Teach or Suggest All of the Claim Limitations

Nonetheless, while Applicant in no way concedes that Examiner's combination of references is proper herein, even if the combination is proper, the cited combination of references, supplementing Neubauer with the use of an antiestrogen to treat prostate cancer, does not teach or suggest all of the limitations of Applicant's claims. Neubauer merely discusses the use of raloxifene as an antimetastatic agent; it does not teach the

use of the present compounds to treat (*e.g.*, stabilize or reduce) AIPC tumors. Again, Raghow and Clinical Trials do not teach the use of an antiestrogen to treat AIPC. Therefore, the combination of references does not teach or suggest all of the claim limitations.

Lastly, since Applicant's claimed methods are patentable, the dependent claims reciting dosage and route of administration are similarly patentable.

In light of the foregoing remarks, Applicant respectfully requests reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a).

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (213) 633-6869.

Respectfully submitted,
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Enclosure: Petition for One-Month Extension of Time
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